THE RELATIONSHIP BETWEEN THE PLASMA CONCENTRATION OF DULOXETINE IN PATIENTS WITH DEPRESSION AND ITS THERAPEUTIC EFFICACY, COMPLIANCE, AND SIDE EFFECTS

NA LI*
Department of psychiatry, the First Affiliated Hospital of Kunming Medical University, Kunming 650032, China

ABSTRACT

Objective: *This study was conducted to analyze the relationship between the plasma concentration of duloxetine in patients with depression (MDD) and its therapeutic effect, compliance, and side effects.*

Methods: *The participants in this study were 100 patients with MDD who visited our hospital between January 2019 and January 2020. They were divided into a low-dose group and a high-dose group and were treated with duloxetine 60 mg/d and 120 mg/d, respectively, for 6 weeks. Fasting venous blood was collected at 1, 3, and 6 weeks after treatment and concentration of duloxetine in the plasma was detected by high-performance liquid chromatography tandem mass spectrometry. Participants completed the Hamilton Inhibition Scale (HAMD) and Hamilton Anxiety Scale (HAMA) before treatment and 1, 3, and 6 weeks after treatment to analyze duloxetine's therapeutic effect. Tess scores were calculated before treatment and 1, 3, and 6 weeks after treatment to compare the drug's side effects between the two groups. The groups' compliance was analyzed before treatment and 1, 3, and 6 weeks after treatment. Pearson linear correlation was used to determine the correlation between plasma concentration and HAMD, HAMA, Tess scores.*

Results: *The plasma concentrations of the high-dose group were significantly higher than those of the low-dose group at all points in time (P<.05). The HAMD scores of the high-dose group were significantly lower than those of the low-dose group at all points in time after treatment (P<.05). The HAMA scores of the high-dose group were significantly lower than those of the low-dose group at all points in time after treatment (P<.05). The Tess scores of the high-dose group were higher than those of the low-dose group at all points in time after treatment (P>.05). There was no significant difference in treatment compliance between the two groups at each point in time (P>.05). There was a significant negative correlation between plasma concentration and HAMD scores at 1, 3, and 6 weeks after treatment in the low-dose group (P < .05). There was a significant negative correlation between plasma concentration and HAMD scores at 1, 3, and 6 weeks after treatment in the high-dose group (P<.05). There was a significant negative correlation between plasma concentration and HAMA scores at 1, 3, and 6 weeks after treatment in the low-dose group (P<.05). There was a significant negative correlation between plasma concentration and HAMD scores at 1, 3, and 6 weeks after treatment in the high-dose group (P<.05).*

Conclusion: *Duloxetine reduced symptoms of depression and anxiety in patients with MDD according to its dose. HAMA and HAMD scores were negatively correlated with duloxetine's plasma concentration. Side effects and patient compliance were not correlated with its plasma concentration.*

Keywords: *Duloxetine, depression, plasma concentration, therapeutic efficacy, compliance, drugs, side effects.*

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Introduction

Depression (MDD) is a common type of mood disorder that is characterized by significantly and persistently low mood. It reduces patients' quality of life, impairs their social lives, and impairs their physical health, leading to greater disability and mortality rates[1]. As the pace of life and pressure that people face increases, so has the incidence of MDD, leading it to become the object of increasing scholarly focus[2]. Duloxetine inhibits the uptake of serotonin and noradrenaline, which are monoamine neurotransmitters, and is used to treat MDD, fibromyalgia, generalized anxiety, stress, urinary incontinence, and other conditions[3]. Duloxetine is effective, safe, and can be administered high doses to treat MDD[4]. However, there have been few studies on the relationship between the plasma concentration of duloxetine and its efficacy in treating MDD. In this study, 100 MDD patients admitted to our

hospital between January 2019 and January 2020 were administered duloxetine to determine how its plasma concentration was related to its therapeutic efficacy, compliance, and side effects.

Materials and methods

General information

The participants in this study were 100 MDD patients admitted to our hospital between January 2019 and January 2020.

To be included, patients had to have:

• Met the diagnostic criteria for MDD in the Diagnostic and Statistical Manual of Mental Disorders[5];

• Scored ≥20 on the Hamilton Inhibition Scale (HAMD);

• Be aged between 18 and 60 years old;

• Have had a first attack or relapse and so have stopped medication for more than 1 month;

• Have received information about the study and signed the informed consent form along with their family members.

Patients were excluded if:

• They had severe physical diseases, neurological diseases, or other mental disorders;

• They had suicidal tendencies;

• Their heart, liver, kidneys, or other important organs had serious dysfunction;

• Were pregnant or lactating.

Patients were divided into a low-dose group and a high-dose group according to their duloxetine dose. This experiment was approved by the hospital ethics committee.

Methods

Patients were administered duloxetine through oxpine tablets, which are coated with duloxetine hydrochloride enteric. Ospin was obtained from Shanghai Sino Western Pharmaceutical Co., Ltd., approval number: National Drug Approval H20061261, product specification: 20 mg* 20S.

Three days before treatment, participants were given 40 mg/d duloxetine through an olespine tablet administered at 8:00 AM and 8:00 PM. On the fourth day, the dosages for both groups were increased. The dosage for the low-dose group was increased to 60 mg/d through 2 olespine tablets administered at 8:00 AM and 1 at 8:00 PM. The dosage for the high-dose group was increased to 120 mg/d through 4 olespine tablets administered 2 at 8:00AM. All patients were treated for 6 weeks.

Metrics

Clinical data

Patient age, gender, body mass index, education level, disease stage, blood, and heart rate were collected.

Plasma detection

Fasting venous blood was collected from patients at 7:00 AM at 1, 3, and 6 weeks after treatment and centrifuged at 3,000 r/min for 10 min. Each patient's plasma was carefully separated into separate groups and refrigerated at -70ºC to avoid repeated freezing and thawing. The plasma concentration of duloxetine was determined by high-performance liquid chromatography tandem mass spectrometry.

HAMD score

The HAMD includes 24 items measuring symptoms of depression, such as anxiety and somatization, weight, cognitive impairment, day-night changes, blockages, sleep disorders, and feelings of hopelessness. Scores over 35 are classified as reflecting major depression while those below 8 are classified as not reflecting depression.

Hamilton Anxiety Scale (HAMA) score

The HAMA includes 14 items, each of which can receive 0-4 points. Scores 29 or above are classified as reflecting severe anxiety, of 21 or above as obvious anxiety, of 14 or above as existing anxiety, of 7 or above as possible anxiety, and of 6 or less as no anxiety.

Treatment Side Effects Scale (TESS) score:

The severity of behavioral toxicity, laboratory abnormalities, neurological symptoms, autonomic nervous symptoms, and cardiovascular symptoms were evaluated on a 0-4 scale in which 0 was asymptomatic, 1 was very mild or indefinite symptoms, 2 was mild symptoms, 3 was moderate symptoms, and 4 was severe symptoms.

Compliance

Complete compliance was defined as taking medication on time.

Partial compliance was defined as not taking medication on time, requiring reminders to take medication on time, or requiring supervision to take the medication. Non-compliance was defined as not taking the medication.

Statistical analyses

SPSS v. 20.0 was used to analyze the data. All values in this paper are expressed as mean ± standard deviation. t-tests were used to compare groups. Enumeration data are expressed as percentages and were compared between groups using χ^2 tests.

The correlations between the plasma concentration of duloxetine and HAMD, HAMA, and TESS scores were determined by conducting Pearson linear correlation tests. Results were considered statistically significant if P<.05.

Results

Descriptive statistics

There were no significant differences in age, body mass index, gender, education level, disease stage, blood pressure, or heart rate between the two groups (P>.05) (Table 1).

Clinical data		Low-dose group (n = 50)	High-dose group (n = 50)	t/χ^2	*P*
Age		36.45±10.25	37.49±11.08	0.487	.627
Body mass index		21.86±2.49	22.41±1.73	1.282	.202
Gender	Male	16 (32.00%)	18 (36.00%)	0.178	.672
	Female	34 (68.00%)	32 (64.00%)		
Education level	Primary school	9 (18.00%)	10 (20.00%)	0.219	.974
	Middle school	17 (34.00%)	16 (32.00%)		
	College	20 (40.00%)	19 (38.00%)		
	None	4 (8.00%)	5 (10.00%)		
Disease stage		14.56±12.48	13.29±12.23	0.513	.608
Blood pressure	Systolic	107.49±7.45	110.54±11.05	1.618	.108
	Diastolic	75.46±7.45	74.15±7.84	0.856	.398
Heart rate		72.64±4.15	71.06±9.45	1.082	.281

Table 1: Descriptive statistics. Data is given as mean ± standard deviation or mean (percentage).

Duloxetine plasma concentration

The high-dose group had significantly higher plasma concentrations of duloxetine than the low-dose group at all points in time (P<.05) (Table 2).

HAMD scores

The HAMD scores of the high-dose group were significantly lower than those of the low-dose group at all points in time after treatment (P<.05) (Table 3).

Time	Low-dose group (n = 50)	High-dose group (n = 50)	*t*	*P*
After 1 week	39.85±20.15	85.95±67.45	4.630	<.001
After 3 weeks compared with the value after 1 week	51.46±32.15[a]	90.89±70.56[a]	3.595	<.001
After 6 weeks compared with the value after 3 weeks	56.79±25.16[ab]	93.87±51.26[ab]	4.591	<.001

Table 2: Duloxetine blood concentrations. Data is given as mean ± standard deviation.
[a]P<.05, [b]P<.05.

Time	Low-dose group (n = 50)	High-dose group (n = 50)	*t*	*P*
Before treatment	31.52±5.64	30.85±3.46	0.716	.475
After 1 week	26.85±2.45[a]	22.79±3.84[a]	6.302	<.001
After 3 weeks compared with the value for week 1	18.26±3.46[ab]	14.84±2.46[ab]	5.696	<.001
After 6 weeks when compared with the value for week 3	11.46±4.29[ab]	9.23±5.46[ab]	2.270	.025

Table 3: HAMD scores. Data is given as mean ± standard deviation.
[a]P<.05, [b]P<.05.

HAMA scores

The HAMA scores for the high-dose group were significantly lower than those for the low-dose group at all points in time after treatment (P<.05) (Table 4).

HAMA score	Low-dose group (n = 50)	High-dose group (n = 50)	*t*	*P*
Before treatment	17.84±6.23	16.89±3.45	0.943	.347
Treatment for 1 week	13.78±4.16[a]	11.52±2.89[a]	3.154	.002
After 3 weeks compared with the value for week 1	9.79±4.02[ab]	7.99±3.45[ab]	2.402	.018
After 6 weeks when compared with the value for week 3	7.86±2.16[ab]	5.26±2.16[ab]	6.018	<.001

Table 4: HAMA scores. Data is given as mean ± standard deviation.
[a]P<.05, [b]P<.05.

Side effects

Forty-four patients had side effects from the duloxetine (Table 5).

TESS scores

The TESS scores for the high-dose group were higher than those for the low-dose group at all points in time after treatment, but this difference was not statistically significant (P>.05) (Table 6).

Compliance

There was no significant difference in compliance between the two groups at each point in time (P>.05) (Table 7).

Side effect	Number of cases	Percentage
Dry mouth	4	4.00%
Constipation	2	2.00%
Reduced appetite	6	3.00%
Dizziness or anemia	4	4.00%
Nausea and vomiting	5	5.00%
Tachycardia	7	7.00%
Abdominal distension	5	5.00%
Increased sweating	5	5.00%
Sleep disorders	6	6.00%
Total number	44	44.00%

Table 5: Incidence of side effects.

TESS score	Low-dose group (n = 50)	High-dose group (n = 50)	*t*	*P*
Before treatment	0.96±1.60	1.18±1.05	0.812	.418
After 1 week compared with the value for before treatment	0.76±0.62a	0.95 ± 0.46a	1.740	.085
After 3 weeks when compared with the value for week 1	0.60±0.25ab	0.62 ± 0.19ab	0.450	.653

Table 6: TESS scores. Data is given as mean ± standard deviation.
[a]P<.05, [b]P<.05.

Group	Compliance level	1 week	3 weeks	6 weeks
Control group (n = 50)	Compliant	28 (56.00%)	22 (44.00%)	18
	Partially compliant	17 (34.00%)	18 (36.00%)	20
	Non-compliant	5 (10.00%)	10 (20.00%)	12
Observation group (n = 50)	Compliant	31 (62.00%)	29 (58.00%)	25
	Partially compliant	16 (32.00%)	17 (34.00%)	20
	Non-compliant	3 (6.00%)	4 (8.00%)	5
χ^2		0.682	3.560	4.021
P		.710	.168	.133

Table 7: Compliance. Data is presented as number (percentage).

Duloxetine plasma concentration and HAMD scores

There was a significant negative correlation between plasma concentration and HAMD scores at 1, 3, and 6 weeks after treatment in the low-dose group (r = -0.378, -0.546, and -0.629, respectively, P<.05) (Table 8). There was a significant negative correlation between plasma drug concentration and HAMD scores at 1, 3, and 6 weeks after treatment in the high-dose group (r = -0.468, -0.328, and -0.506, respectively, P<.05) (Table 8).

		1 week	3 weeks	6 weeks
Low-dose group	Plasma concentration	39.85±20.15	51.46±32.15	56.79±25.16
	HAMD scores	26.85±2.45	18.26±3.46	11.46±4.29
r		-0.378	-0.546	-0.629
P		.026	<.001	<.001
High-dose group	Plasma concentration	85.95±67.45	90.89±70.56	93.87±51.26
	HAMD score	22.79±3.84	14.84±2.46	9.23±5.46
r		-0.468	-0.328	-0.506
P		<.001	.008	<.001

Table 8: Correlations between medication concentration and HAMD scores. Data is given as mean ± standard deviation.

Correlation between plasma concentration and HAMA scores

There was a significant negative correlation between plasma concentration and HAMA scores at 1, 3, and 6 weeks after treatment in the low-dose group (r = -0.541, -0.387, and -0.451, respectively, P<.05) (Table 9). There was a significant negative correlation between plasma concentration and HAMD scores at 1, 3, and 6 weeks in the high-dose group (r = -0.528, -0.467, and -0.389, respectively, P<.05) (Table 9).

		1 week	3 weeks	6 weeks
Low-dose group	Plasma concentration	39.85±20.15	51.46±32.15	56.79±25.16
	HAMA scores	13.78±4.16	9.79±4.02	7.86±2.16
r		-0.541	-0.387	-0.451
P		<.001	.034	<.001
High-dose group	Plasma concentration	85.95±67.45	90.89±70.56	93.87±51.26
	HAMA score	11.52±2.89	7.99±3.45	5.26±2.16
r		-0.528	-0.467	-0.389
P		<.001	<.001	<.001

Table 9: Correlations between drug concentration and HAMA scores. Data is given as mean ± standard deviation.

Correlation between plasma concentration and TESS scores

There was no significant correlation between plasma concentrations and TESS scores at 1, 3, and 6 weeks after treatment in either group (P>.05) (Table 10).

		1 week	3 weeks	6 weeks
Low-dose group	Plasma concentration	39.85±20.15	51.46±32.15	56.79±25.16
	TESS scores	0.96±1.60	0.76±0.62	0.60±0.25
r		-0.485	-0.115	-0.362
P		.095	.665	.229
High-dose group	Plasma concentration	85.95±67.45	90.89±70.56	93.87±51.26
	TESS score	1.18±1.05	0.95±0.46	0.62±0.19
r		-0.056	-0.168	-0.089
P		.853	.569	.954

Table 10: Correlations between plasma concentration and TESS scores. Data is given as mean ± standard deviation.

Discussion

MDD is a common chronic mental disease that is characterized by repeated recurrences lasting two weeks and up to several years and is the second-most burdensome disease in China[6]. At present, medication, psychotherapy, and physical therapy are common clinical methods for treating MDD, though drug therapy has become the preferred method in recent years with the in-depth study of selective serotonin reuptake inhibitors[7].

Duloxetine is a new type of antidepressant that has been studied in recent years and has a significant anti-depressant effect on both 5-hydroxytryptamine and norepinephrine[8]. It has relatively little affinity for M receptors and little effect on the cognitive functioning of patients[9].Therapeutic drug monitoring is conducted to manage patients' adverse and toxic reactions to drugs. It detects the concentration of a given drug in the blood. This information can be used to improve dosages to ensure that the drug remains at an appropriate concentration in the blood, optimizing treatment. It is often used with patients with reduced liver and kidney functioning, children, and the elderly, all of whom are prone to toxic reactions[10-13]. However, duloxetine's antidepressant effect is not clear.

The HAMD is commonly used to evaluate depression severity. HAMD scores can be used to determine the degree to which a drug is affecting the target symptoms[14]. The HAMA is mainly used to evaluate the severity of anxiety in adult patients and is widely used in clinical psychiatry due to its reliability and validity[15]. In this study, HAMD and HAMA scores were used to evaluate the efficacy of duloxetine in treating MDD. The results showed that the high-dose group had significantly lower HAMD and HAMA scores than the low-dose group at all points in time. This result suggests that both high and low doses of duloxetine are effective in treating MDD, though the higher dose was more effective. This result was similar to the results of Wang et al[16].The TESS is used to evaluate adverse reactions to drugs. It is the most complete scale of this type and includes common adverse reactions, indications of reactions, and laboratory examination indicators[17].

In this study, there was no statistically significant difference in the strength of the correlations between TESS scores and compliance between the two groups. These results suggest that duroxeline plasma concentration in MDD patients did not affect the side effects they experienced and their compliance. Thus, any change in patient compliance may have been a product of the fact that they did not understand the treatment methods or were worried about the drug's side effects.

In order to analyze the relationship between the plasma concentration of duloxetine in MDD patients and its therapeutic effects and side effects, Pearson linear correlation analyses were conducted. The results showed that plasma concentration was significantly negatively correlated with both HAMD and HAMA scores in both groups at all points in time after treatment. There was no significant correlation between plasma concentrations and TESS scores in either group at each point in time after treatment. This result suggests that detecting duloxetine plasma concentrations and rapidly reaching of the target plasma concentration can improve duloxetine's effectiveness.

This study showed that different doses of duloxetine can reduce depression and anxiety symptoms in MDD patients. The results showed that duloxetine plasma concentration was negatively correlated with HAMA and HAMD scores but was not correlated with side effects or patient compliance.

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Corresponding Author:
Na Li
Email: g0941a@163.com
(China)